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Prognostic significance of systemic inflammatory markers in laryngeal squamous cell carcinoma

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Abstract

Aim: The aim of this study is to reveal the relationship between neutrophil-lymphocyte ratio (NLR), Mean platelet volume (MPV), Platelet- lymphocyte ratio (PLR), MPV-platelet ratio (MPVPR) and systemic inflammatory index (SII) levels in laryngeal Squamous cell carcinoma.

Material and Methods: One hundred twenty patients diagnosed with larynx cancer between 2014 and 2019 were evaluated retrospectively. In addition, 30 patients without cancer were included in the study as a control group. The patients 'ages, genders and preoperative blood tests, pathology results (tumor stage and lymph node metastasis) were obtained from the patients' files. In addition, NLR, PLR, MPVPR, Systemic inflammatory index (SII) values were calculated and recorded.

Results: There was a significant positive correlation between stage and NLR, PLR and SII values, and a significant negative correlation between MPVPR (p=0,001, r: 0,292, p=0,009, r: 0,238, p=0,000, r: 0,384, p=0,004, r: -0,259, respectively). There was a significant positive correlation between metastasis status and NLR, PLR and SII values (p=0,013, r: 0,226, p=0,032, r: 0,196, p=0,003, r: 0,268, respectively). In terms of metastasis, sensitivity 63,2%, and specificity 58,5% for NLR (p=0,014), sensitivity 63,2% and specificity 58,5% for PLR (p=0,033), sensitivity 68,4% and specificity 65,2% for SII (p=0,001) were found. The cut-off point for these values was >2.33, >113.7, and >646.28, respectively.

Discussion: Our study is the first study to assess that WBC, NLR, PLR, and SII parameters can be used as a potential prognosis factor in patients with laryngeal tumors in predicting tumor stage and evaluating metastasis status.

Keywords

Laryngeal cancer; Prognostic factor; Neutrophil-Lymphocyte ratio; Platelet- Lymphocyte ratio; MPV-Platelet ratio; Systemic inflammatory index

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Introduction

Laryngeal cancer accounts for 2.4% of all newly diagnosed malignancies each year in the world [1]. Laryngeal cancer is the second most common head and neck cancer other than skin cancer and accounts for 25% of all head and neck cancers [2]. Almost all (95%) are squamous cell carcinomas. Laryngeal cancers are more common in middle-aged men. Risk factors include smoking, tobacco, alcohol use, air pollution and occupational factors [3]. This type of head and neck cancer responds best to treatment when appropriate diagnosis and adequate treatment approaches are applied.

The TNM classification and histological rating system provide guidance for determining tumor behavior and treatment method for larynx cancer. The general condition and profession of the patient are other important parameters that determine which treatment method will be applied and how much of the larynx functions can be maintained. However, despite the application of the same treatment method in patients with similar features, obtaining different results shows that all these parameters are not sufficient, and direct us to investigate different prognostic factors. The purpose of investigating different tumor markers in larynx cancer is to improve cancer preventive treatments, increase the knowledge about cancer and the biological behavior of the host, predict the recurrence and secondary cancers encountered in larynx cancer, and plan the treatments more effectively [1-3].

The relationship between inflammation and cancer has been known since ancient times [4]. Inflammatory cells, together with the cytokines and chemokines they produce in the early stages of the neoplastic process, increase genomic instability and angiogenesis, facilitate tumor cell migration, increase DNA damage, and thus become a strong tumor promoter [4]. In recent studies, it has been shown that pre-treatment peripheral leukocyte (neutrophil, lymphocyte monocyte) and platelet levels are related to diagnosis and prognosis in various cancers [5-7]. Besides, it is also an inexpensive and convenient biomarker. The pre-treatment neutrophil/lymphocyte ratio (NLR) has been shown to be a poor prognostic factor in patients with renal cell cancer, small and non-small cell lung cancer [6]. However, NLR was shown to be related with many malignancies such as nasopharyngeal, gastric, hepatocellular, pancreatic and epithelial ovarian cancer [8, 9]. In addition, mean platelet volume (MPV), platelet/lymphocyte ratio (PLR), MPV-platelet ratio (MPVPR) and systemic inflammatory index (SII) levels have been shown to vary in various tumors and are associated with prognosis [10, 11]. However, there are a limited number of studies on larynx cancer in the literature.

The aim of this study is to reveal the relationship between NLR, MPV, PLR, MPVPR and systemic inflammatory index (SII) levels and squamous cell cancer of the larynx.

Material and Methods

The study was carried out after receiving the approval of the institutional Ethics Committee. In our study we conducted a retrospective analysis of 120 patients who applied to the Otorhinolaryngology Clinic of the Gaziantep University Research Hospital and underwent partial or total laryngectomy for laryngeal cancer between 2014 and 2019. In addition, 30 patients without cancer were included in the study as a control group. Patients with active infection, hematological diseases, second primary cancer, and chronic inflammatory diseases such as systemic lupus erythematosus (SLE) and missing data were excluded from the study.

The patients 'ages, genders and preoperative blood tests, pathology results (tumor stage and lymph node metastasis) were obtained from the patients' files. In addition, NLR, PLR, MPVPR, Systemic inflammatory index (SII) values were calculated and recorded. The following parameters were calculated from the hemogram results performed at the preoperative stage: NLR was found by dividing the neutrophil count by the lymphocyte count; PLR was found by dividing platelet count by lymphocyte count; MPVPR was found by dividing the number of MPV by the number of platelets; Systemic inflammatory index (SII) was found by multiplying neutrophil count and PLR value.

The tumor classification of the patients was made according to the TNM classification determined by The American Joint Committee on Cancer (AJCC), which was modified in 2017. The stage of the tumor and lymph node involvement were evaluated based on histopathological evaluation. Analyzes of all samples were performed on Sysmex XN-9100TM (Kobe, Japan) hematological auto analyzer devices.

Statistical analysis

The normality control of the data was done with the Shapiro Wilk test. The Student's t- test was used for comparing the means of normally distributed parameters, and the Mann-Whitney U test was used for the comparison of parameters that did not conform to normal distribution. In multiple comparisons, the Kruskal-Wallis variance analysis was used. Descriptive statistics were expressed with Odds ratio and 95% confidence intervals. ROC analysis was used to determine the cut-off point, the area under the curve (AUC), the sensitivity (sensitivity) and the specificity (specificity) of the data. $P < 0.05$ was considered statistically significant.

Results

The comparison of laboratory and socio-demographic findings between the groups of patients and control is shown in Table 1. The average age of the patients was 62.00 (34.0-79.0) years, and the number of males was 112 (93.3%). In the control group, the mean age was 53.00 (36.0-65.0) years, and the number of males was 112 (93.3%). There was a statistically significant difference between the groups in terms of age and gender (p=0,000). Compared to the control group, WBC, RBC and Neutrophil levels were statistically significantly higher in the patient group (p=0,004, p=0,000, p=0,003, respectively). Hemoglobin and Hematocrit levels were statistically significantly lower in the patient group compared to the control group (p=0,010, p=0,000, respectively). Compared to the control group, NLR, PLR and SII values were statistically significantly higher in the patient group (p=0,006, p=0,030, p=0,042, respectively). No statistical significance was found between the groups in terms of other parameters (Table 1).

The comparison of laboratory results according to the cancer stage is shown in Table 2. There was a statistically significant difference between groups in terms of WBC, platelet, and neutrophil levels (p=0,001, p=0,020, and p=0,009, respectively).

Table 1. Comparison of laboratory and socio-demographic findings

	Patient (n=120)	Control (n=30)	P value
Age (years)	62,00 (34,0-79,0)	53,00 (36,0-65,0)	0,000
Gender			
male	112 (93,3%)	24 (86,7%)	0,021
female	8 (6,7%)	4 (13,3%)	
WBC (/mm3)	9,29 (5,4-24,9)	8,12 (5,5-13,8)	0,004
RBC (µL)	5,00 (2,1-6,8)	5,45 (4,7-5,9)	0,000
Hemoglobin (g/dl)	14,90 (9,6-17,9)	15,65 (13,5-17,2)	0,010
Hematocrit (%)	43,95 (26,5-53,9)	46,60 (42,4-52,6)	0,000
MCV (fL)	88,85 (57,7-121,6)	86,55 (77,9-94,6)	0,204
MCH (pg)	29,80 (19,2-44,0)	28,90 (25,2-31,0)	0,212
MCHC (g/dl)	33,55 (30,0-86,7)	33,25 (31,0-36,1)	0,589
RDW (%)	13,30 (11,7-20,3)	12,90 (11,8-15,3)	0,256
Platelet (/mm3)	262,50 (124,0-555,0)	271,50 (162,0-372,0)	0,311
MPV (fL)	9,90 (7,4-12,8)	10,25 (9,1-11,7)	0,105
Neutrophil (/mm3)	5,73 (2,9-65,8)	4,95 (2,9-8,1)	0,003
Lymphocyte (/mm3)	2,32 (0,22-20,80)	2,45 (1,61-4,63)	0,190
NLR	2,30 (0,28-41,77)	1,98 (0,94-3,80)	0,006
PLR	111,68 (16,3-736,3)	108,61 (39,2-182,3)	0,030
MPVPR	0,037 (0,017-0,098)	0,037 (0,025-0,070)	0,928
SII	604,14 (104,2-8026,6)	522,36 (245,4-1176,3)	0,042

WBC: White blood cell; RBC: Red blood cell; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; RDW: Red cell distribution width; MPV: Mean platelet volume; NLR: neutrophil-lymphocyte ratio; PLR: Platelet- lymphocyte ratio; MPVPR: MPV-platelet ratio; SII: Systemic inflammatory index.

Table 2. Comparison of laboratory results according to cancer stage

	T1 (n=30)	T2 (n=30)	T3 (n=30)	T4 (n=30)	P value
WBC (/mm3)	8,31 (5,4-11,8)	9,02 (5,5-24,6)	9,53 (5,7-13,7)	9,99 (6,5-19,9)	0,001
RBC (µL)	5,20 (4,3-6,8)	4,93 (3,9-5,5)	4,92 (3,8-6,2)	4,92 (2,18-6,08)	0,061
Hemoglobin (g/dl)	15,30 (12,4-17,6)	14,80 (11,8-16,7)	14,80 (11,7-17,9)	14,35 (9,6-16,7)	0,020
Hematocrit (%)	45,50 (38,1-51,9)	43,50 (36,5-47,9)	44,35 (34,9-53,9)	42,15 (26,5-50,4)	0,031
MCV (fL)	88,10 (60,3-94,8)	89,50 (76,3-97,0)	89,15 (73,9-96,7)	87,70 (57,7-121,6)	0,474
MCH (pg)	29,75 (19,5-33,3)	29,80 (23,7-33,7)	30,40 (22,7-33,5)	28,80 (19,2-44,0)	0,233
MCHC (g/dl)	33,55 (32,1-35,2)	33,40 (30,0-35,7)	33,80 (30,7-36,9)	33,35 (30,8-86,7)	0,173
RDW (%)	13,20 (12,2-20,3)	13,25 (11,9-19,9)	13,20 (11,7-18,8)	13,40 (11,9-18,3)	0,862
Platelet (/mm3)	243,50 (124,0-329,0)	260,0 (193,0-533,0)	265,50 (178,0-431,0)	292,0 (162,0-555,0)	0,009
MPV (fL)	10,10 (7,9-12,2)	9,75 (7,4-12,8)	10,00 (8,9-12,2)	9,45 (8,5-11,5)	0,187
Neutrophil (/mm^3)	4,58 (2,9-8,2)	5,33 (2,92-20,69)	6,16 (3,1-65,8)	7,16 (3,8-13,8)	0,000
Lymphocyte (/mm^3)	2,18 (0,53-4,37)	2,25 (0,52-10,70)	2,33 (0,53-4,40)	2,44 (0,22-20,80)	0,994
NLR	1,99 (0,81-15,62)	1,97 (0,82-19,92)	2,66 (1,23-28,24)	3,10 (0,28-41,77)	0,017
PLR	96,39 (54,5-520,7)	113,85 (42,2-565,3)	115,58 (52,2-611,3)	154,80 (16,3-736,3)	0,038
MPVPR	0,041 (0,02-0,09)	0,035 (0,01-0,06)	0,039 (0,021-0,068)	0,031 (0,017-0,069)	0,010
SII	453,7 (205,0-4311,8)	558,9 (177,2-4662,0)	657,6 (284,8-8026,6)	995,2 (104,2-6767,1)	0,000

WBC: White blood cell; RBC: Red blood cell; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; RDW: Red cell distribution width; MPV: Mean platelet volume; NLR: neutrophil-lymphocyte ratio; PLR: Platelet- lymphocyte ratio; MPVPR: MPV-platelet ratio; SII: Systemic inflammatory index.

Table 3. Logistic regression analysis of factors used to differentiate malign tumor from benign tumor

	β	(95% CI)	P value
WBC (/mm^3)	0,234	(0,012-0,059)	0,004
Neutrophil (/mm^3)	0,081	(-0,006-0,019)	0,325
Platelet (/mm^3)	0,130	(0,000-0,002)	0,113
NLR	0,195	(0,003-0,030)	0,017
PLR	0,221	(0,000-0,002)	0,006
MPVPR	-0,127	(-9,449-1,115)	0,121
SII	0,001	(1,000-1,001)	0,007

WBC: White blood cell; NLR: neutrophil-lymphocyte ratio; PLR: Platelet- lymphocyte ratio; MPVPR: MPV-platelet ratio; SII: Systemic inflammatory index.

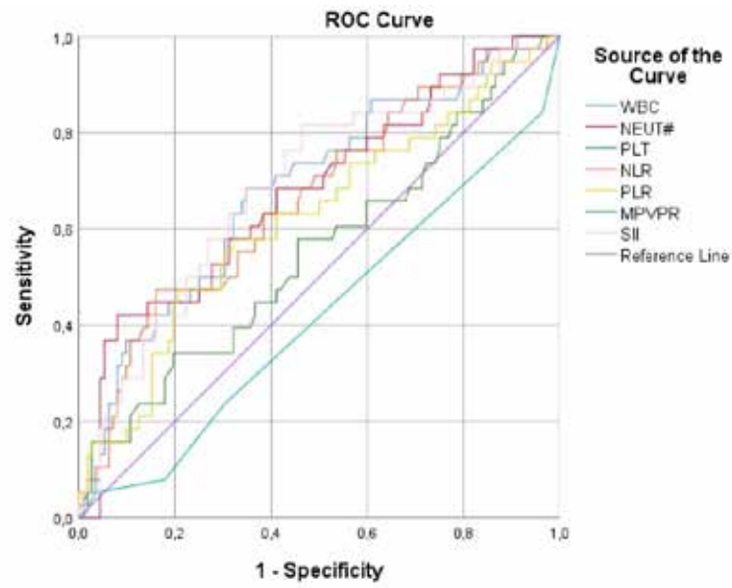

Figure 1. ROC analysis results in patients with metastases (WBC: White blood cell; NEUT#: Neutrophil (/mm^3); PLT: Platelet; NLR: neutrophil-lymphocyte ratio; PLR: Platelet- lymphocyte ratio; MPVPR: Mean Platelet Volume-platelet ratio; SII: Systemic inflammatory index)

WBC, platelet and neutrophil levels increased as the stage increased. There was a statistically significant difference between the groups in terms of hemoglobin and hematocrit levels (p=0,020, p=0,031, respectively). It was found that hemoglobin and hematocrit levels decreased as the stage increased. However, statistical significance was found between the groups in terms of NLR, PLR, MPVPR, and SII parameters (p=0,017, p=0,038, p=0,010 and p=0,000, respectively). In addition, as the stage increased, it was determined that NLR, PLR and SII levels increased and MPVPR level decreased (Table 2).

In the comparison of laboratory results and treatment methods applied according to metastasis status in patients, WBC and Neutrophil levels were found to be statistically significantly higher in patients with metastasis compared to patients without metastasis (p=0,006, p=0,010, respectively). Compared to the group without metastasis, NLR, PLR, SII values were statistically significantly higher in the group with metastasis (p=0,014, p=0,033, and p=0,003, respectively). No statistical

significance was found between the groups in terms of other biochemical parameters (p = 0,863). Partial laryngectomy in 43 (35.8%), radiotherapy in 27 (22.5%) and total laryngectomy in 50 (41.7%) cancer patients were performed. Partial laryngectomy in 28 (34.1%), radiotherapy treatment in 27 (32.9%) and total laryngectomy in 27 (32.9%) patients without metastasis were performed. Partial laryngectomy in 15 (39.5%) and total laryngectomy in 23 (60.5%) patients with metastasis were performed. Statistical significance was found in terms of treatments applied to patients with and without metastasis (p=0,000).

In correlation analysis of results according to the stage and metastasis, there was a significant positive correlation between stage and metastasis, WBC, platelet, neutrophil values (p=0,000, r: 0,481, p=0,000, r: 0,370, p=0,002, r: 0,275, p=0,000, r: 0,446, respectively). However, there was a significant positive correlation between stage and NLR, PLR and SII values and a negative correlation with MPVPR (p=0,001, r: 0,292, p=0,009, r: 0,238, p=0,000, r: 0,384, p=0,004, r: -0,259, respectively). There was a significant positive correlation between metastasis status and WBC and neutrophil values (p=0,006, r: 0,252, p=0,009, r: 0,237, respectively). However, there was a significant positive correlation between metastasis status and NLR, PLR and SII values (p=0,013, r: 0,226, p=0,032, r: 0,196, p=0,003, r: 0,268, respectively).

According to the results of ROC analysis in patients with metastasis, sensitivity 68,4%, and specificity 63,4% for WBC (p=0,001), sensitivity 63,2%, and specificity 58,9% for neutrophil (p=0,001), sensitivity 63,2%, and specificity 59,8% for NLR (p=0,003), sensitivity 63,2% and specificity 58,5% for PLR (p=0,023), sensitivity 68,4% and specificity 65,2% for SII (p=0,001) were found. The cut-off point for these values were >9.32, >5.75, >2.36, >113.7, and >646.28, respectively. As a result, according to ROC analysis for metastasis, platelet and MPVPR were not found to be prognostic factors, although the WBC, Neutrophil, NLR, PLR and SII were significant prognostic factors (Figure 1).

Logistic regression analysis of factors used for differentiating malign tumors from benign tumors is shown in Table 3. Risk factors that were found to be significantly associated with differentiation in the regression analysis included WBC, NLR, PLR, and SII (Table 3).

Discussion

In our study, a statistically significant relationship was found between the stage of cancer and the platelet, neutrophil, NLR, PLR, MPVPR and systemic inflammatory index (SII) levels in patients with laryngeal squamous cell carcinoma. In our study, however, a statistically significant relationship was found between metastasis and especially NLR, PLR and SII levels in patients with laryngeal cancer metastasized.

The relationship between cancer and chronic inflammation began about a hundred years ago, when Rudolf Virchow first identified leukocytes in tumor tissue [12, 13]. Since then, many studies have been conducted showing that chronic inflammation in tumor tissue as a host response is effective in tumor development, metastasis, prognosis and response to treatment. In recent studies, the relationship between systemic inflammation degree and cancer has been shown by evaluating parameters such as NLO, PLR and SII, which are systemic inflammatory markers [5, 14]. While neutrophils and platelets contain and secrete inflammatory factors that inhibit apoptosis in tumor cells, directly contribute to the proliferation and metastasis of tumor cells, lymphocytes release protective inflammatory factors that prevent proliferation and metastasis [5, 12, 13, 15, 16]. Lymphocytopenia, which occurs in the tumor tissue, also causes the immune response to be interrupted by the host [17]. NLR, PLR and SII will be higher and MPVPR will be lower due to the increase in the number of neutrophil-platelets and decreased lymphocyte systemically [18-20]. In our study, neutrophil, NLR, PLR and SII values were found to be statistically significantly higher in patients with laryngeal cancer. In addition, although the platelet, MPV and lymphocyte values were high and the MPVPR value was low in the patient group, it was not statistically significant.

In a study by Murat et al., elevated NLR might be an inflammatory marker to differentiate low- from high-grade malignant parotid gland tumors [5]. In another study, it is stated that NLR and PLR parameters can be used in the differential diagnosis of benign and malignant masses in patients with parotid gland tumors [10]. Rachidi et al. reported that neutrophil, lymphocyte and NLR have prognostic significance in these cancers in large cohort studies involving all head and neck cancers (oral, pharyngeal and laryngeal cancers [21]. In studies on tongue squamous cell cancers, Öztürk et al. reported that NLR and PLR values are valuable markers in predicting local recurrence, and Deveci et al. reported that high SII values were associated with increased perineural/lymphovascular invasion and extranodal involvement [14, 22]. Chen et al. reported that PLR is superior to NLR in predicting disease-free survival and overall survival in oral squamous cell cancers [15]. In a study by Mori et al., it was stated that NLR may be a prognostic factor in patients with gastric cancer [23]. In the same study, no significant correlation was found between PLR and gastric cancer patients as prognostic factors [23]. In our study, as tumor stage increased, WBC, platelet, Neutrophil, NLR, PLR and SII levels increased and MPVPR level decreased. However, WBC, Neutrophil, NLR, PLR and SII values were statistically significantly higher in patients with metastasis. Furthermore, according to ROC analysis for metastasis, platelet and MPVPR were not found to be prognostic factors, although the WBC, Neutrophil, NLR, PLR and SII were significant prognostic factors.

In the literature, studies examining the relationship of laryngeal tumors with inflammatory markers are limited. Studies on patients with larynx cancer have also reported that NLR, MPV and PLR are independent prognostic inflammatory markers. In a study conducted by Fu et al., MPV level was found to be decreased in patients with laryngeal cancer, and was reported to be a prognostic factor [11]. In our study, no significant relationship was detected between the groups in terms of MPV level. However, there was no significant relationship in terms of tumor stage and metastasis in the patient group. Kum et al. reported that in patients with laryngeal squamous cell carcinoma and precancerous laryngeal lesions, the NLR levels were significantly higher than in patients with benign laryngeal lesions [24]. In a study by Chen et al., the elevated preop PLR

and NLR were significantly related with cancer progression and worse survival [15]. In the same study, it was stated that the preoperative NLR could be independent prognostic markers of overall survival (OS) and progression-free survival (PFS) in laryngeal squamous cell carcinoma patients undergoing surgical resection [15]. In a study by Kara et al. on 81 patients with laryngeal cancer, the mean PLR in the T4 stage tumors were significantly higher than the T1 and T2 stage, and according to ROC analysis for mortality, although the PLR and RDW were significant prognostic factors, NLR was not found to be a prognostic factor [25]. In the study conducted by Erdis et al., it was seen that high SII value may be an indicator of shorter overall survival and disease-free survival in patients with oral cavity cancer [29]. In our study, NLR, PLR and SII values were found statistically significantly higher in 120 patients with laryngeal cancer. However, a significant positive correlation was found between tumor stage and NLR, PLR and SII values, and a negative correlation with MPVPR. In addition, there was a significant positive correlation between the presence of metastasis and NLR, PLR and SII values. Moreover, according to the results of ROC analysis in patients with metastasis, sensitivity 68,4% and specificity 63,4% for WBC (p=0,001), sensitivity 63,2% and specificity 58,9% for neutrophil (p=0,001), sensitivity 63,2% and specificity 59,8% for NLR (p=0,003), sensitivity 63,2% and specificity 58,5% for PLR (p=0,023), sensitivity 68,4% and specificity 65,2% for SII (p=0,001) were found. The cut-off point for these values were >9.32, >5.75, >2.36, >113.7, and >646.28, respectively. As a result, according to ROC analysis for metastasis, platelet and MPVPR were not found to be prognostic factors, although the WBC, Neutrophil, NLR, PLR and SII were significant prognostic factors. However, as a result of logistic regression analysis of factors used for differentiating malign tumor from benign tumor, the risk factors found to be significantly associated with differentiation in the regression analysis included WBC, NLR, PLR, and SII. Thus, we determined that WBC, NLR, PLR, and SII were significant prognostic factors for metastasis.

Our study has some limitations. First, our study is a single-center and retrospective study. The small patient sample size was the second limitation. Moreover, multi-center and prospective studies should be planned to support these preliminary results.

Conclusion

Our study is the first study to assess WBC, NLR, PLR, and SII parameters can be used as potential prognosis factors in patients with laryngeal tumors, in predicting tumor stage and evaluating metastasis status. These cheap and easy parameters can be used as potential prognosis factors in patients with laryngeal tumors to predict tumor stage and evaluate metastasis status. We think that these values should be defined in laboratory devices and added to blood results in order to facilitate the clinician's work. However, new prospective studies with a larger group of patients are needed to determine the reference intervals of these values and to use them as prognostic factors.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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